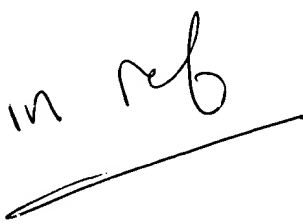




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

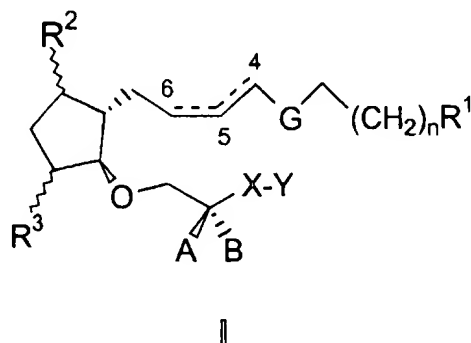
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(21) International Application Number: PCT/US98/25681 (22) International Filing Date: 4 December 1998 (04.12.98) (30) Priority Data: 60/068,461 22 December 1997 (22.12.97) US (71) Applicant (for all designated States except US): ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): FENG, Zixia [CN/US]; 4204 Hideaway Drive, Arlington, TX 76017 (US). HELLBERG, Mark, R. [US/US]; 5211 Overridge Drive, Arlington, TX 76017 (US). (74) Agents: COPELAND, Barry, L. et al.; Alcon Laboratories, Inc., Patent Dept., Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).		(81) Designated States: AU, BR, CA, JP, MX, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report. With amended claims and statement. 

(54) Title: 13-OXA PROSTAGLANDINS FOR THE TREATMENT OF GLAUCOMA AND OCULAR HYPERTENSION**(57) Abstract**

13-Oxa analogs of certain prostaglandins and methods of their use in treating glaucoma and ocular hypertension are disclosed.

WHAT IS CLAIMED IS:

1. A method of treating glaucoma or ocular hypertension in a patient, which comprises administering to the patient a pharmaceutically effective amount of a compound of formula II:



wherein:

$R^1 = CO_2R$, $CONR^4R^5$, CH_2OR^6 , or $CH_2NR^7R^8$; where:

$R = H$ or cationic salt moiety, or CO_2R forms a pharmaceutically acceptable ester moiety;

$R^4, R^5 = \text{same or different} = H$ or alkyl; $R^6 = H$, acyl, or alkyl;

$R^7, R^8 = \text{same or different} = H$, acyl, or alkyl; with the proviso that if one of R^7 ,

$R^8 = \text{acyl}$, then the other $= H$ or alkyl;

$n = 0$ or 2 ;

$G = CH_2$ or O ;

$R^2, R^3 = \text{same or different} = OH$, acyloxy, alkoxy, carbonyl, halogen, H , with the proviso

that at least one of $R^2, R^3 = OH$, acyloxy, alkoxy, or carbonyl;

---- = single or non-cumulated double bond;

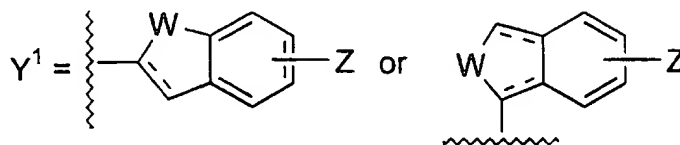
one of A, B = H, the other = halo, OH, acyloxy, alkoxy;

or A-B = O(CH₂)₂O or double bonded O;

X = (CH₂)_q or (CH₂)_qO; where q = 1-6; and

Y = a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, alkoxy, acyl, acyloxy, amino, alkylamino, acylamino, or hydroxy; or

X-Y = (CH₂)_pY¹; where p = 0-6; and



wherein:

W = CH₂, O, S(O)_m, NR⁹, CH₂CH₂, CH=CH, CH₂O, CH₂S(O)_m, CH=N, or CH₂NR⁹; where m = 0-2, and R⁹ = H, alkyl, or acyl;

Z = H, alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy; and

---- = single or double bond, or

X-Y = cyclohexyl or cyclopentyl.

2. The method of claim 1, wherein the compound is administered topically.
3. The method of claim 2, wherein the compound is administered as a solution, suspension, or emulsion in an ophthalmically acceptable vehicle.
4. The method of claim 2, wherein the concentration of the compounds is between about 0.00003 to about 0.5 weight percent.
5. The method of claim 4, wherein the concentration of the compounds is between about 0.0005 to about 0.03 weight percent.
6. The method of claim 5, wherein the concentration of the compounds is between about 0.005 to about 0.05 weight percent.

7. The method of claim 1, wherein:

$R^1 = CO_2R$, where $R = H$ or CO_2R forms a pharmaceutically acceptable ester moiety;

$n = 0$;

$G = CH_2$;

$R^2 = R^3 = OH$ in the α configuration, or $R^2 = O$ (as a carbonyl) and $R^3 = OH$ in the α configuration or H ;

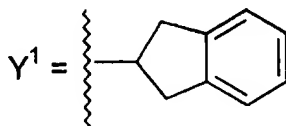
---- = single or non-cumulated double bond, with the proviso that a double bond between carbons 4 and 5 may not be of the *trans* configuration;

one of $A, B = H$, the other = halo or OH ;

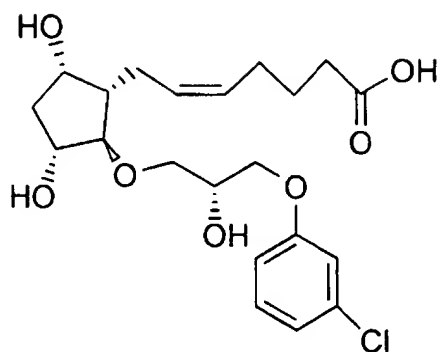
$X = (CH_2)_2$ or CH_2O ; and

$Y = \text{phenyl}$, optionally substituted with halo or trihalomethyl; or

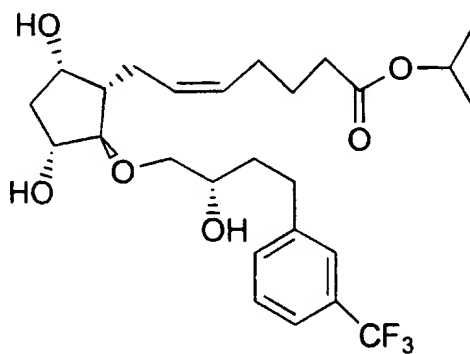
$X-Y = Y^1$; where



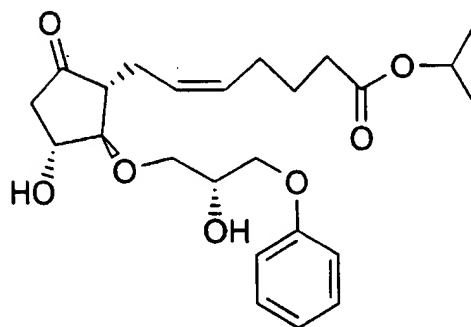
8. The method of claim 7, wherein the compound is:



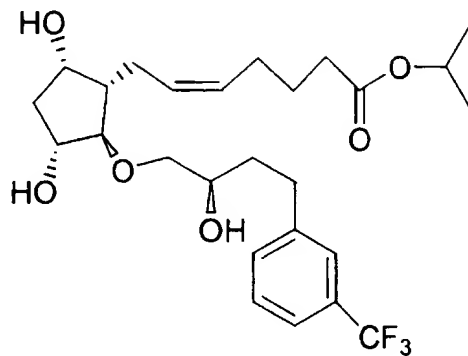
9. The method of claim 7, wherein the compound is:



10. The method of claim 7, wherein the compound is:



11. The method of claim 7, wherein the compound is:



12. The method of claim 1, wherein:

$R^1 = \text{CO}_2\text{R}$, where $\text{R} = \text{H}$ or alkyl;

$n = 0$;

$\text{G} = \text{O}$;

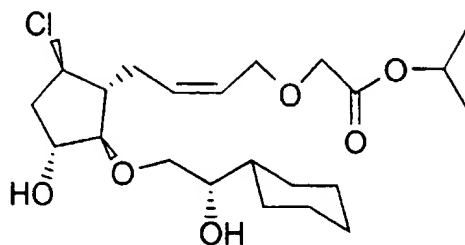
$\text{R}^2 = \text{Cl}$ in the β configuration, and $\text{R}^3 = \text{OH}$ in the α configuration;

---- = single or double bond, with the proviso that a single bond exists between carbons 4 and 5;

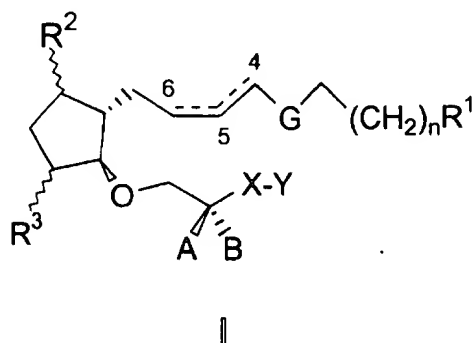
one of A, B = H, the other = halo or OH;

X-Y = cyclohexyl.

13. The method of claim 12, wherein the compound is:



14. A compound of formula I:



wherein:

$R^1 = \text{CO}_2R$, CONR^4R^5 , CH_2OR^6 , or $\text{CH}_2\text{NR}^7R^8$; where:

$R = \text{H}$ or cationic salt moiety, or CO_2R forms a pharmaceutically acceptable ester moiety;

$R^4, R^5 = \text{same or different} = \text{H or alkyl}$; $R^6 = \text{H, acyl, or alkyl}$;

$R^7, R^8 = \text{same or different} = \text{H, acyl, or alkyl}$; with the proviso that if one of R^7 ,

$R^8 = \text{acyl}$, then the other $= \text{H or alkyl}$;

$n = 0 \text{ or } 2$;

$G = \text{CH}_2 \text{ or } \text{O}$;

R^2, R^3 = same or different = OH, acyloxy, alkoxy, carbonyl, halogen, H, with the proviso that at least one of R^2, R^3 = OH, acyloxy, alkoxy, or carbonyl;

---- = single or non-cumulated double bond;

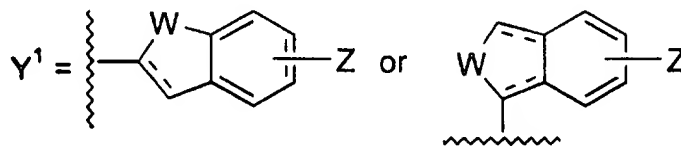
one of A, B = H, the other = halo, OH, acyloxy, alkoxy;

or A-B = $O(CH_2)_2O$ or double bonded O;

$X = (CH_2)_q$ or $(CH_2)_qO$; where $q = 1-6$; and

Y = a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, alkoxy, acyl, acyloxy, amino, alkylamino, acylamino, or hydroxy; or

$X-Y = (CH_2)_p Y^1$; where $p = 0-6$; and



wherein:

$W = CH_2, O, S(O)_m, NR^9, CH_2CH_2, CH=CH, CH_2O, CH_2S(O)_m, CH=N,$
or CH_2NR^9 ; where $m = 0-2$, and $R^9 = H, \text{alkyl, or acyl}$;

$Z = H, \text{alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy; and}$



---- = single or double bond; or

X-Y = cyclohexyl or cyclopentyl.

15. The compound of claim 14, wherein for formula I:

$R^1 = CO_2R$, where $R = H$ or CO_2R forms a pharmaceutically acceptable ester moiety;

$n = 0$;

$G = CH_2$;

$R^2 = R^3 = OH$ in the a configuration, or $R^2 = O$ (as a carbonyl) and $R^3 = OH$ in the a configuration or H;

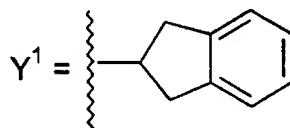
---- = single or non-cumulated double bond;

one of A, B = H, the other = halo or OH;

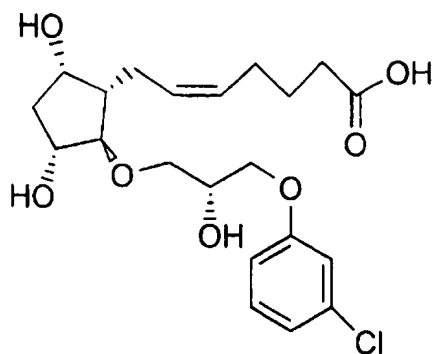
$X = (CH_2)_2$ or CH_2O ; and

Y = phenyl, optionally substituted with halo or trihalomethyl; or

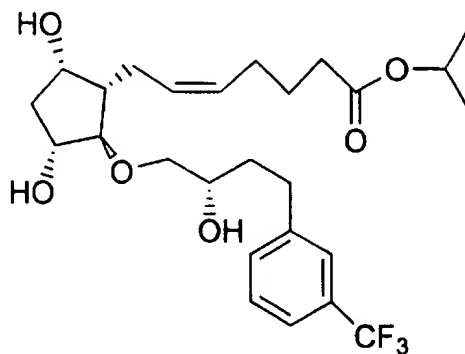
$X-Y = Y^1$; where



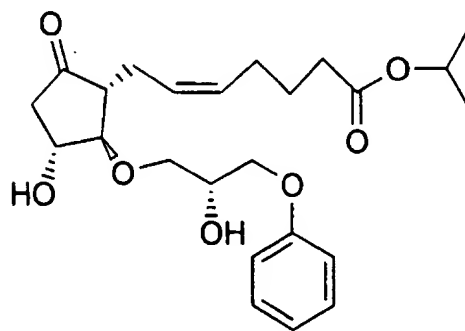
16. The compound of claim 15, having the formula:



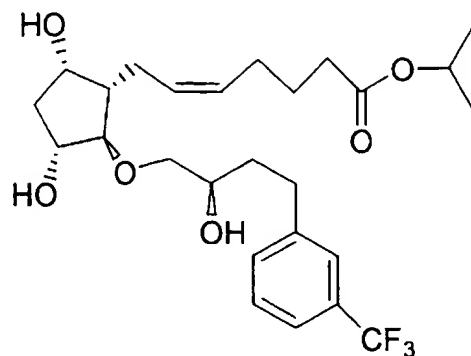
17. The compound of claim 15, having the formula:



18. The compound of claim 15, having the formula:



19. The compound of claim 15, having the formula:



20. The compound of claim 14, wherein for formula I:

$R^1 = \text{CO}_2\text{R}$, where $\text{R} = \text{H}$ or alkyl CO_2R forms a pharmaceutically acceptable ester moiety;

$n = 0$;

$\text{G} = \text{O}$;

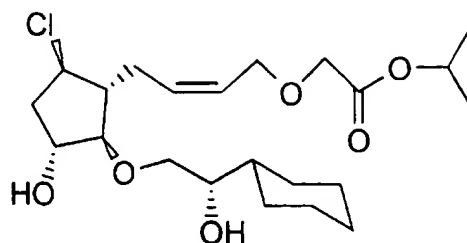
$\text{R}^2 = \text{Cl}$ in the β configuration, and $\text{R}^3 = \text{OH}$ in the α configuration;

---- = single or double bond, with the proviso that a single bond exists between carbons 4 and 5;

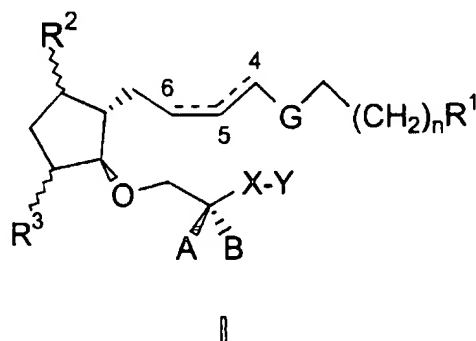
one of A, B = H, the other = halo or OH;

X-Y = cyclohexyl.

21. The compound of claim 20, having the formula:



22. An ophthalmic composition for the treatment of glaucoma and ocular hypertension, comprising a compound of formula II:



wherein:

$R^1 = \text{CO}_2\text{R}$, CONR^4R^5 , CH_2OR^6 , or $\text{CH}_2\text{NR}^7\text{R}^8$; where:

$\text{R} = \text{H}$ or cationic salt moiety, or CO_2R forms a pharmaceutically acceptable ester moiety;

$\text{R}^4, \text{R}^5 = \text{same or different} = \text{H or alkyl}$; $\text{R}^6 = \text{H, acyl, or alkyl}$;

$\text{R}^7, \text{R}^8 = \text{same or different} = \text{H, acyl, or alkyl}$; with the proviso that if one of R^7 ,

$\text{R}^8 = \text{acyl}$, then the other = H or alkyl ;

$n = 0$ or 2 ;

$G = \text{CH}_2$ or O ;

$R^2, R^3 = \text{same or different} = \text{OH, acyloxy, alkoxy, carbonyl, halogen, H, with the proviso that at least one of } R^2, R^3 = \text{OH, acyloxy, alkoxy, or carbonyl}$;

---- = single or non-cumulated double bond;

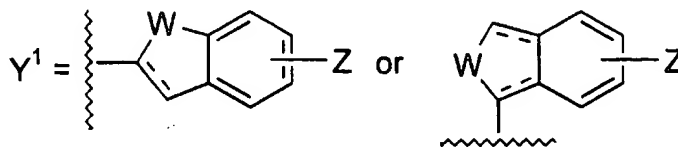
one of $A, B = \text{H}$, the other = halo, OH, acyloxy, alkoxy;

or $A-B = \text{O}(\text{CH}_2)_2\text{O}$ or double bonded O ;

$X = (\text{CH}_2)_q$ or $(\text{CH}_2)_q\text{O}$; where $q = 1-6$; and

$Y = \text{a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, alkoxy, acyl, acyloxy, amino, alkylamino, acylamino, or hydroxy; or}$

$X-Y = (\text{CH}_2)_p Y^1$; where $p = 0-6$; and



wherein:

$W = \text{CH}_2, \text{O}, \text{S}(\text{O})_m, \text{NR}^9, \text{CH}_2\text{CH}_2, \text{CH}=\text{CH}, \text{CH}_2\text{O}, \text{CH}_2\text{S}(\text{O})_m, \text{CH}=\text{N},$
 or CH_2NR^9 ; where $m = 0-2$, and $R^9 = \text{H, alkyl, or acyl}$;



Z = H, alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy; and

---- = single or double bond; or

X-Y = cyclohexyl or cyclopentyl.

23. The composition of claim 22, wherein for formula I:

$R^1 = CO_2R$, where R = H or alkyl;

$n = 0$;

$G = CH_2$;

$R^2 = R^3 = OH$ in the α configuration, or $R^2 = O$ (as a carbonyl) and $R^3 = OH$ in the α configuration or H;

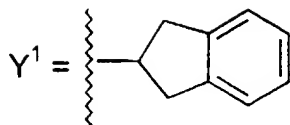
---- = single or non-cumulated double bond;

one of A, B = H, the other = halo or OH;

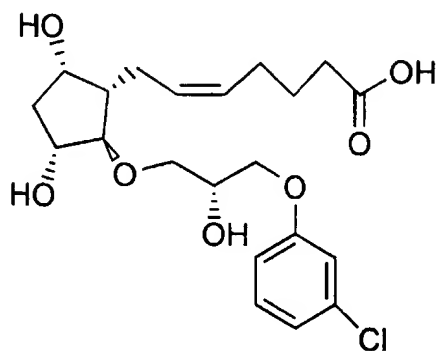
$X = (CH_2)_2$ or CH_2O ; and

Y = phenyl, optionally substituted with halo or trihalomethyl; or

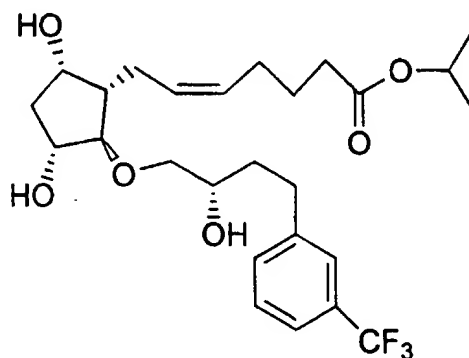
X-Y = Y¹; where



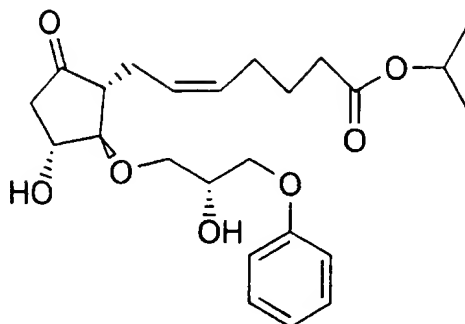
24. The composition of claim 23, having the formula:



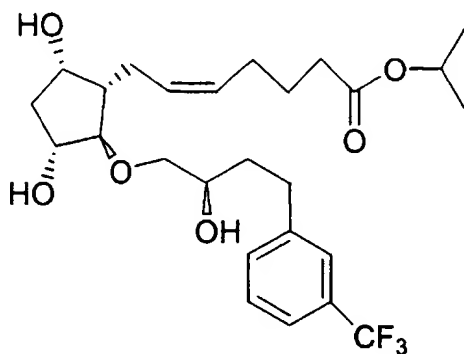
25. The composition of claim 23, having the formula:



26. The composition of claim 23, having the following formula:



27. The composition of claim 23, having the following formula:



28. The composition of claim 22, wherein for formula I:

$R^1 = \text{CO}_2\text{R}$, where $\text{R} = \text{H}$ or CO_2R forms a pharmaceutically acceptable ester moiety;

$n = 0$;

$\text{G} = \text{O}$;

$\text{R}^2 = \text{Cl}$ in the β configuration, and $\text{R}^3 = \text{OH}$ in the α configuration;

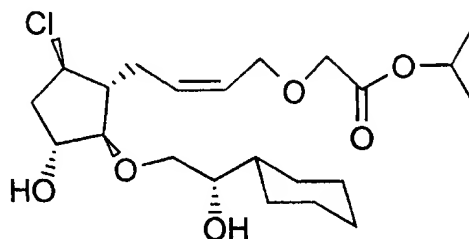


---- = single or double bond, with the proviso that a single bond exists between carbons 4 and 5;

one of A, B = H, the other = halo or OH; and

X-Y = cyclohexyl.

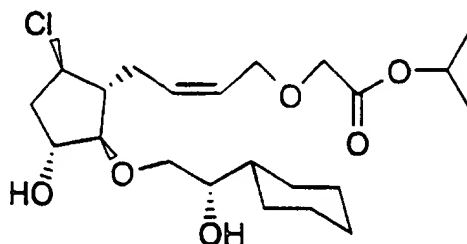
29. The composition of claim 28, having the following formula:



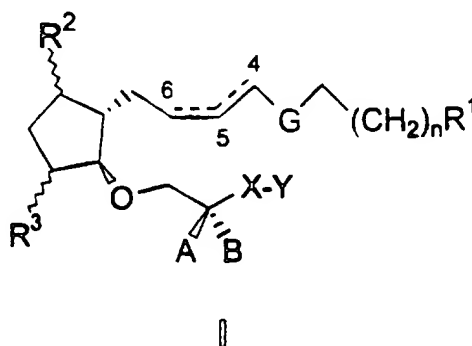
AMENDED CLAIMS

[received by the International Bureau on 17 May 1999 (17.05.99);
original claim 18 cancelled; original claims 14 and 15 amended;
remaining claims unchanged (6 pages)]

13. The method of claim 12, wherein the compound is:



14. A compound of formula I:



wherein:

$R^1 = \text{CO}_2\text{R}$, CONR^4R^5 , CH_2OR^6 , or $\text{CH}_2\text{NR}^7\text{R}^8$; where:

$\text{R} = \text{H}$ or cationic salt moiety, or CO_2R forms a pharmaceutically acceptable ester moiety;

$\text{R}^4, \text{R}^5 = \text{same or different} = \text{H}$ or alkyl; $\text{R}^6 = \text{H}$, acyl, or alkyl;

$\text{R}^7, \text{R}^8 = \text{same or different} = \text{H}$, acyl, or alkyl; with the proviso that if one of R^7 ,

$\text{R}^8 = \text{acyl}$, then the other = H or alkyl;

$n = 0$ or 2 ;

$\text{G} = \text{CH}_2$ or O ;

$\text{R}^2, \text{R}^3 = \text{same or different} = \text{OH}$, acyloxy, alkoxy, carbonyl, halogen, H , with the proviso that at least one of $\text{R}^2, \text{R}^3 = \text{OH}$, acyloxy, alkoxy, or carbonyl;

$\text{—} = \text{single or non-cumulated double bond}$;

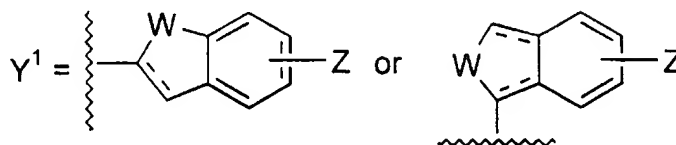
one of A, B = H, the other = halo, OH, acyloxy, alkoxy;

or A-B = O(CH₂)₂O or double bonded O;

X = (CH₂)_q or (CH₂)_qO; where q = 1-6; and

Y = a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, alkoxy, acyl, acyloxy, amino, alkylamino, acylamino, or hydroxy; or

X-Y = (CH₂)_pY¹; where p = 0-6; and



wherein:

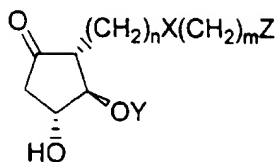
W = CH₂, O, S(O)_m, NR⁹, CH₂CH₂, CH=CH, CH₂O, CH₂S(O)_m, CH=N, or CH₂NR⁹; where m = 0-2, and R⁹ = H, alkyl, or acyl;

Z = H, alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy; and

---- = single or double bond; or

X-Y = cyclohexyl or cyclopentyl;

with the proviso that the following compounds be excluded:



wherein:

$Z = \text{CH}_2\text{OH}$, CONHR^1 , or CO_2R^2 ;

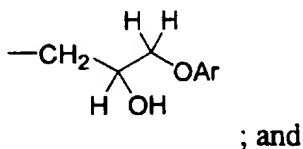
$\text{R}^1 = \text{H}$ or alkyl;

$\text{R}^2 = \text{H}$, optionally substituted phenyl or naphthyl, C_{1-6} alkyl, C_{7-10} phenalkyl, and physiologically acceptable salts;

$n = 1$ and $m = 3$ or 5 ; or $n = 2$ and $m = 2$ or 4 ;

$X = \text{CH}_2\text{CH}_2$, or *cis*- or *trans*- $\text{CH}=\text{CH}$;

$Y =$



Ar = a phenyl ring, optionally substituted with alkyl, halo, trihalomethyl, or alkoxy.

15. The compound of claim 14, wherein for formula I:

$\text{R}^1 = \text{CO}_2\text{R}$, where $\text{R} = \text{H}$ or CO_2R forms a pharmaceutically acceptable ester moiety;

$n = 0$;

$G = CH_2$;

$R^2 = R^3 = OH$ in the α configuration, or $R^2 = O$ (as a carbonyl) and $R^3 = OH$ in the α configuration or H;

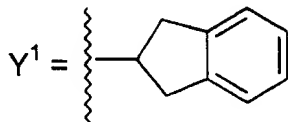
$\text{---} =$ single or non-cumulated double bond;

one of A, B = H, the other = halo or OH;

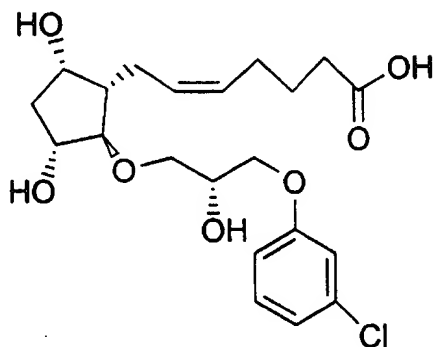
$X = (CH_2)_2$ or CH_2O ; and

$Y =$ phenyl, optionally substituted with halo or trihalomethyl; or

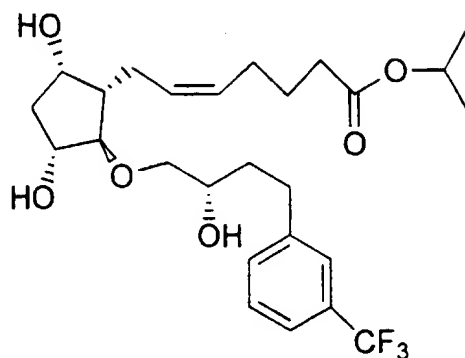
$X-Y = Y^1$; where



16. The compound of claim 15, having the formula:

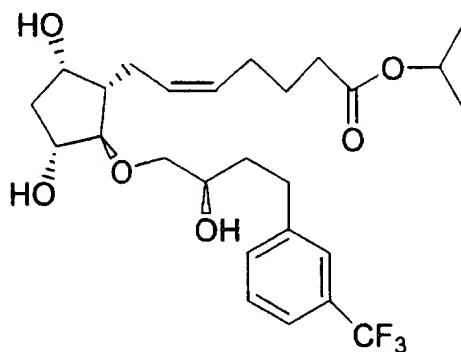


17. The compound of claim 15, having the formula:



18. [Cancelled]

19. The compound of claim 15, having the formula:



20. The compound of claim 14, wherein for formula I:

$R^1 = CO_2R$, where $R = H$ or alkyl CO_2R forms a pharmaceutically acceptable ester moiety;

$n = 0$;

$G = O$;

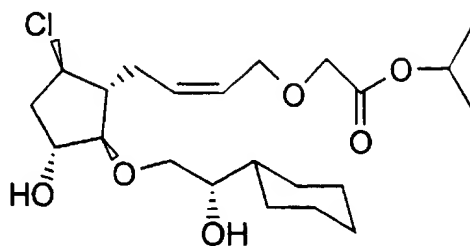
$R^2 = Cl$ in the β configuration, and $R^3 = OH$ in the α configuration;

$\text{---} =$ single or double bond, with the proviso that a single bond exists between carbons 4 and 5;

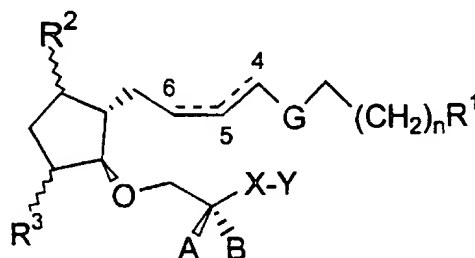
one of A, B = H, the other = halo or OH;

X-Y = cyclohexyl.

21. The compound of claim 20, having the formula:



22. An ophthalmic composition for the treatment of glaucoma and ocular hypertension, comprising a compound of formula I:



I

wherein:

$R^1 = CO_2R, CONR^4R^5, CH_2OR^6, \text{ or } CH_2NR^7R^8$; where:

$R = H$ or cationic salt moiety, or CO_2R forms a pharmaceutically acceptable ester moiety;

$R^4, R^5 = \text{same or different} = H$ or alkyl; $R^6 = H, \text{ acyl, or alkyl}$;

$R^7, R^8 = \text{same or different} = H, \text{ acyl, or alkyl}$; with the proviso that if one of R^7 ,

$R^8 = \text{acyl, then the other} = H$ or alkyl;



STATEMENT UNDER ARTICLE 19

The amendments (and in the case of claim 18, its cancellation) are intended to avoid any overlap between the composition of matter claims and the disclosures of the Category X references cited in the International Search Report. Specifically, the amended claims expressly exclude the compounds disclosed in the cited references.

INTERNATIONAL SEARCH REPORT

Intern ☐ Application No
PCT/US 98/25681

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C405/00 A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 265 248 A (GLAXO GROUP LTD) 27 April 1988 see examples 1-3 ---	14,15, 20,22, 23,28
X	DE 36 13 573 A (GLAXO GROUP LTD) 30 October 1986 see examples 1-13 ---	14,15, 20,22, 23,28
X	EP 0 160 495 A (GLAXO GROUP LTD) 6 November 1985 cited in the application see examples 1-23 ---	14,15, 20,22, 23,28
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

8 March 1999

Date of mailing of the international search report

17.03.99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040. Tx. 31 651 epo nl,

Authorized officer

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/25681

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 23223 A (ALCON LAB INC ;SELLIAH ROBERT D (US); HELLBERG MARK R (US); KLIMKO) 3 July 1997 see the whole document -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/25681

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1 to 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC1/US 98/25681

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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